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MANEC Urethra

Mixed adenoneuroendocrine carcinoma of the urethra

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Introduction

Primary urethral cancer is one of the rarest urogenital tumours with an incidence of 1.3 per million population(1). Recent epidemiological studies have shown that transitional cell carcinoma (TCC)remains the most common pathology, accounting for between 55%-65% of cases of urethral. The majority of remaining cases are due to squamous cell carcinoma (SCC) (16-21%) and adenocarcinomas (10-16%)(1, 2). In general, urethral carcinomas are aggressive tumours that typically present late and with relatively poor outcomes. Adenocarcinomas, like those found in the bladder, usually arise due to chronic irritation and inflammation with resultant intestinal metaplasia of the urothelium. In very rare cases, adenocarcinomas may display diverse types of differentiation and even coexist with other tumour types including neuroendocrine tumours(3). Whilst there have been a limited number of reports of Mixed Adenoneuroendocrine Carcinoma (MANEC) of the bladder, we report the first case of a primary MANEC of the urethra.

Case Report

A 62-year-old woman was referred to the urology team with a suburethral mass found during investigation for vaginal prolapse. The patient was otherwise well with no significant past medical history. The patient had noted the mass for a number of years but it had increased in size over the previous few months prompting referral to the gynaecology team.

On review by a urologist, the patient reported some difficulty in voiding and post terminal dribbling. Examination revealed a smooth, firm mass extending from the bladder neck to urethral meatus. Cystoscopy showed a dilated urethra with normal mucosa and normal bladder. Magnetic resonance imaging (MRI) of the pelvis showed diffuse thickening of the urethra with high T2 signals. Appearances were initially suggestive of a periurethral diverticulum. Following discussion by the gynaecological and urological multi-disciplinary oncology meetings, the most likely differential diagnosis was a urethral diverticulum. The patient underwent an open excision of the urethral mass and urethral reconstruction which was performed without complication. An irregular urethral mass was excised and the urethra closed over a catheter. The patient was discharged on day two and the catheter removed after six weeks.

Histopathological assessment of the specimen showed a mucinous adenocarcinoma with neuroendocrine differentiation. Tumour cells were positive with CK20, CEA, Ca 19.9 and synaptophysin. They were negative for ER, PR, CA125, Ck7, chromogranin.. Staging CT thorax/abdomen/pelvis and FDG CT PET both showed mediastinal lymphadenothy with

increased FDG uptake and further uptake in the oesophagus. OGD excluded metastatic oesophageal disease. A video-assisted thorascopic surgery (VATS) procedure and biopsy similarly confirmed benign disease in the mediastinum secondary to thymic follicular hyperplasia.

Following discussion with the patient , a radical urethrectomy, vaginal reconstruction and Mitrofanoff urinary diversion was performed. Patient developed small bowel ileus which was managed conservatively and was discharged after 11 days post operatively. Post operatively histology confirmed a MANEC. Immunohistochemisty suggested an intestinal phenotype and malignant cells were CDX-2 positive. Tumour was present at the bladder margin and circumferential margins. Adjuvant FOLFOX (folinic acid, fluorouracil, oxaliplatin) chemotherapy was recommended but the patient refused and remains under observation.

Discussion

A rare diagnosis, MANEC is most commonly found in the gastrointestinal tract. According to WHO criteria, the adenocarcinomatous and neuroendocrine components must each represent 30% of the tumour(4). Prior to the recognition of MANEC as a separate clinical entity and WHO classification, the variety of definitions and designations used of the tumour led to considerable confusion in the literature. These tumours have been found to be generally aggressive with poor outcomes. Multimodal therapy has been found to offer a survival benefit with treatment directed to the most aggressive component of tumour(5). Given the variability of outcomes seen with MANEC, further attempts have been made to further subcategorise them as low, medium and high-grade tumours. The degree of differentiation may relate to clinical outcomes with high grade tumours being more aggressive and having poorer outcomes(5).

There have been a number of reports of MANEC of the urinary bladder. The lack of a WHO definition for MANEC of the urinary tract and variation in definitions and terminology, hinders accurate evaluation of the prevalence. A greater number of neuroendocrine tumours have been reported and frequently an admixture of other cell lines is seen, most commonly TCC(6, 7). The presence of large proportions of neuroendocrine and adenocarcinoma remains rare. In the majority of cases they are associated with the urachus(8-10). Whilst adenocarcinomas arise due to intestinal metaplasia of the urothelium, neuroendocrine cells have been described in normal transitional epithelium and may then provide the origin for small cell bladder tumours(11). In cases of coexisting adenocarcinomas, it is believed that small cell tumours arise from the neuroendocrine cells within the area of intestinal metaplasia(3).

Clinically urethral tumours present late. Especially for adenocarcinomas, there is a wide variation in presenting signs and symptoms making diagnosis difficult. Most commonly patients present with irritative voiding symptoms and dyspareunia(12). Important initial investigations include direct visualisation, US and MRI of the pelvis. MRI has been shown to have a higher specificity over ultrasound and is recommend as first line imaging alongside for CT for distant spread(12, 13).

Diagnosis relies on pathological assessment which can be difficult and require subspecialist input. Whilst pure neuroendocrine tumours can be diagnosed on light microscopy, immunophenotyping is usually required to confirm the diagnosis. Neuroendocrine markers such as synaptophysin, seen in this case, and chromogranin are typically positive. CK20 positivity has also been associated with neuroendocrine tumours of the bladder. In contrast immunohistochemistry is of limited benefit in adenocarcinoma where clinicopathological correlation is the main stay of diagnosis. In cases of mixed tumours, the proportion of individual tumours components can be clinically important. Within the bladder both adenocarcinomas and neuroendocrine carcinomas are typically aggressive with high metastatic potential and poorer prognosis than TCC. Tumours with small cell elements are considerably more aggressive(6). Similarly, in other organs such as the prostate, there is evidence to suggest that neuroendocrine differentiation has negative prognostic significance(14).

Given the very limited experience of MANEC tumours of the urinary tract, treatment is predominantly guided by expert opinion. A multidisciplinary approach is essential for a accurate and timely diagnosis. Histopathological diagnosis can be difficult and involving teams experienced in managing neuroendocrine tumours at an early stage is important. Experience from the GI tract has shown that MANEC require multimodal treatment. Where possible, radical excision is usually recommended. Firstline chemotherapy regimens for either the neuroendocrine or non-neuroendocrine component have been found to be equally effective(15). In patients with extensive or metastatic disease, chemotherapy offers the principle modality of treatment. Yet with the uncommonness of the disease, there is little evidence on which to base treatment decisions and, as highlighted in this case, it is important to reach a joint decision on management plans with the patient.

MANECs are very uncommon tumours and we present the first reported case of a MANEC of the urethra. Successful management of such uncommon diagnoses necessitate a multidisciplinary approach with the early involvement of surgeons, oncologists, histopathologist and radiologist. Early and close engagement with the patient is also critical especially when treatment decisions must be made on expert opinion.

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